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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/765,668	01/27/2004	David B. Rozema	Mirus.042.02	9890

25032 7590 10/01/2008

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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	PAPER NUMBER
1636	
MAIL DATE	DELIVERY MODE
10/01/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/765,668	ROZEMA ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,7,8,12,16,17,21 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,7,8,12,16,17,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the amendment, filed 7/1/2008, in which claims 5 and 12 were amended. Currently, claims 5, 7, 8, 12, 16, 17, 21 and 22 are pending.

Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

Response to Arguments - 35 USC § 112

The rejection of claims 5, 7, 8, 12, 16, 17, 21 and 22 under 35 U.S.C. 112, second paragraph, has been withdrawn in view of Applicant's amendment to the claims in the reply filed 7/1/2008.

Response to Arguments - 35 USC § 102

The rejection of claims 5, 7, 8 and 21 under 35 U.S.C. 102(e) as being anticipated by Adams et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 7/1/2008. Adams et al do not specifically teach that the water soluble polymer such as a styrene-maleic anhydride, divinylethter-maleic acid or poly(maleic anhydride co-vinyl ether), which is further modified by reacting with hydrophobic alcohols or amines, is a polyanion.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

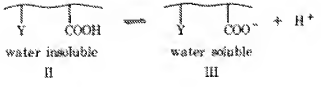
Claims 5, 7, 8 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adams et al (US Patent Application Publication No. 2005/0153926 A1, cited in a prior action; see the entire reference) in view of Heller et al (Journal of Applied Polymer Science, Vol. 22, pages 1991-2009, 1978; see the entire reference). This is a new rejection, necessitated by the amendment of claim 5 to indicate that the polymer is a polyanion.

Adams et al teach a method of delivery a polynucleotide to the cytoplasm of a cell, consisting of (i) forming a composition comprising a water soluble polymer such as styrene-maleic anhydride, divinylether-maleic acid or poly(maleic anhydride-co-vinyl ether) and a nucleic acid linked to the polymer via an ethylene group (a functional group), where the polymer is further modified by reacting with hydrophobic alcohols or amines, and (ii) administering the composition to a cell *in vitro* such that the cell endocytoses the polymer and nucleic acid (e.g. paragraphs [0037], [0057], [0081]-[0084], [0090]-[0093], [0162] and [0171]). Adams et al teach that the ethylene functional group is a reactive group (e.g., paragraph [0013]).

Adams et al do not specifically teach that the water soluble styrene-maleic anhydride polymer, which is further modified by reacting with hydrophobic alcohols or amines, is a polyanion.

Heller et al teach that partially esterified copolymers derived from ethylene-maleic anhydride or methyl vinyl ether-maleic anhydride are readily prepared from commercially available alternating copolymers (e.g., page 1993, 1st full paragraph). Heller et al teach that the

copolymers in the un-ionized state are hydrophobic and water insoluble, but in the ionized state they are water soluble (e.g., page 1993, 2nd full paragraph). The solubilization process is generically represented by Heller et al using the following formula on page 1993:



The copolymer comprises a solubilizing group –COOH and a hydrophobic group Y (e.g., page 1993, 3rd full paragraph). Heller et al teach that the hydrophobic group can be any hydrophobic group (e.g., page 1993, 3rd full paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of delivering a polynucleotide to the cytoplasm of a cell of Adams et al to include the addition of a single hydrophobic group to a maleic acid anhydride moiety as taught by Heller et al because Adams et al teach the reaction of the polymer with a hydrophobic alcohol or amine, and Heller et al it is within the ordinary skill in the art to use any hydrophobic group to react with the anhydride moiety.

One would have been motivated to make such a modification in order to receive the expected benefit of providing a water soluble polymer as taught by Heller et al. Adams et al teach the use of a water soluble polymer such as styrene-maleic anhydride further modified by reacting with hydrophobic alcohols or amines, and Heller et al teach that providing a carboxylic acid group and a hydrophobic group maintains water solubility. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the

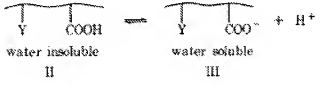
contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 12, 16, 17 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adams et al (US Patent Application Publication No. 2005/0153926 A1, cited in a prior action; see the entire reference) in view of Heller et al (Journal of Applied Polymer Science, Vol. 22, pages 1991-2009, 1978; see the entire reference) and Tonge et al (US Patent No. 6,436,905, cited in a prior action; see the entire reference). This is a new rejection, necessitated by the amendment of claims 5 and 12 to indicate that the polymer is a polyanion.

Adams et al teach a method of delivery a polynucleotide to the cytoplasm of a cell, consisting of (i) forming a composition comprising a water soluble polymer such as styrene-maleic anhydride, divinylether-maleic acid or poly(maleic anhydride-co-vinyl ether) and a nucleic acid linked to the polymer via an ethylene group (a functional group), where the polymer is further modified by reacting with hydrophobic alcohols or amines, and (ii) administering the composition to a cell *in vitro* such that the cell endocytoses the polymer and nucleic acid (e.g. paragraphs [0037], [0057], [0081]-[0084], [0090]-[0093], [0162] and [0171]). Adams et al teach that the ethylene functional group is a reactive group (e.g., paragraph [0013]).

Adams et al do not specifically teach that the water soluble poly(maleic anhydride-co-vinyl ether) polymer, which is further modified by reacting with hydrophobic alcohols or amines, is a polyanion. Further, Adams et al do not specifically teach the poly(maleic anhydride-co-vinyl ether) polymer where the vinyl ether is butyl vinyl ether.

Heller et al teach that partially esterified copolymers derived from ethylene-maleic anhydride or methyl vinyl ether-maleic anhydride are readily prepared from commercially available alternating copolymers (e.g., page 1993, 1st full paragraph). Heller et al teach that the copolymers in the un-ionized state are hydrophobic and water insoluble, but in the ionized state they are water soluble (e.g., page 1993, 2nd full paragraph). The solubilization process is generically represented by Heller et al using the following formula on page 1993:



The copolymer comprises a solubilizing group –COOH and a hydrophobic group Y (e.g., page 1993, 3rd full paragraph). Heller et al teach that the hydrophobic group can be any hydrophobic group (e.g., page 1993, 3rd full paragraph).

Tonge et al teach a composition comprising a synthetic amphipathic polymer, including both hydrophobic groups and anionic hydrophilic groups and acting as a lipid-solubilizing agent (e.g. column 3, lines 49-52). Tonge et al teach that especially suitable polymers may be formed as alternating copolymers of maleic acid (or the anhydride thereof) with styrene, indene or a C_{1-4} alkyl, e.g. methyl substituted styrene or indene, or with propyl (or isopropyl) or butyl vinyl ether (e.g. column 6, lines 27-31, 60-63). Tonge et al disclose examples of suitable polymers, including Poly(maleic anhydride-styrene) (a random copolymer), Poly(maleic anhydride-propyl vinyl ether), and Poly(maleic anhydride-butyl vinyl ether) (e.g. column 6, lines 60-63). Tonge et al teach the use of the polymers to administer drugs or DNA or RNA to cells to facilitate the

uptake of the therapeutic agent into target cells (e.g. column 1, lines 31-45; column 12, line 40 to column 13, line10).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of delivering a polynucleotide to the cytoplasm of a cell of Adams et al to include the addition of a single hydrophobic group to a maleic acid anhydride moiety as taught by Heller et al because Adams et al teach the reaction of the polymer with a hydrophobic alcohol or amine, and Heller et al it is within the ordinary skill in the art to use any hydrophobic group to react with the anhydride moiety. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of delivering a nucleic acid to a cell using a poly(maleic anhydride-co-vinyl ether)-based composition to include butyl vinyl ether as the vinyl ether, which is taught by Tonge et al, because Adams et al and Tonge et al teach it is within the ordinary skill in the art to use poly(maleic anhydride-co-vinyl ether)-based compositions for the delivery of nucleic acid to a cell.

One would have been motivated to make such a modification in order to receive the expected benefit of providing a water soluble polymer as taught by Heller et al. Adams et al teach the use of a water soluble polymer such as poly(maleic anhydride-co-vinyl ether) further modified by reacting with hydrophobic alcohols or amines, and Heller et al teach that providing a carboxylic acid group and a hydrophobic group maintains water solubility. Further, one would have been motivated to make such a modification in order to receive the expected benefit of defining the complete structure of the poly(maleic anhydride-co-vinyl ether) with a vinyl ether suitable for the delivery of nucleic acid as taught by Tonge et al. Based upon the teachings of the

cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments - 35 USC § 103

The rejection of claims 12, 16, 17 and 22 under 35 U.S.C. 103(a) as being unpatentable over Adams et al in view of Tonge et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 7/1/2008. Adams et al and Tonge et al do not specifically teach that the polymer is a polyanion.

With respect to the rejections presented above, Applicant's arguments filed 7/1/2008 have been fully considered but they are not persuasive.

The response asserts that Adams et al teach that the polymer is a polycation having membrane activity. The response specifically points to paragraphs [0136], and [0147]-[0151] of Adams et al. This is not found persuasive, because those portions of the Adams reference refer to polylysine as a polycationic polymer for polynucleotide delivery. The rejection is based on the teachings of Adams et al that are directed to poly(maleic anhydride-co-vinyl ether) and poly(styrene-maleic anhydride) polymers (e.g., paragraphs [0083] and [0084]). The rejection is not based upon the use of polylysine as a polymer in the method. Further, the response asserts that Adams et al do not teach a polyanion that is membrane active at pH 6.5. Where the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of the claimed product. See

In re Ludtke 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 U.S.C. 102, or "prima facie obviousness" under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). In the instant case, the references teach polymers that meet the structural limitations of the claims and, absent any evidence to the contrary, would necessarily be capable of lysing membranes at pH 6.5.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached at 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Dunston, Ph.D.
Examiner
Art Unit 1636

/JD/

/Celine X Qian Ph.D./
Primary Examiner, Art Unit 1636